

Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the above-identified application:

1. **(Withdrawn)** A glycosylated molecule or molecular complex that comprises at least a portion of a human beta secretase binding pocket, wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by the structure coordinates listed in Table 1.
2. **(Withdrawn)** The molecule or molecular complex of claim 1, wherein the binding pocket comprises the amino acids listed in Table 6.
3. **(Withdrawn)** The molecule or molecular complex of claim 1, wherein the binding pocket comprises the amino acids listed in Table 7.
4. **(Withdrawn)** A molecule or molecular complex that is structurally homologous to a human beta secretase molecule or molecular complex that forms a crystal having unit cell dimensions $a=112.0 \pm 35$ Å, $b=112 \pm 35$ Å, $c=110 \pm 35$ Å, $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$, wherein the human beta secretase molecule or molecular complex is represented by at least a portion of the structure coordinates listed in Table 1.
5. **(Withdrawn)** A scalable three-dimensional configuration of points, at least a portion of said points derived from structure coordinates of at least a portion of a human beta secretase molecule or molecular complex listed in Table 1 comprising at least one of a human beta secretase or beta secretase-like binding pocket, wherein the human beta secretase molecule or molecular complex forms a crystal having the trigonal space group symmetry $P3_221$.

6. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 5, wherein substantially all of said points are derived from structure coordinates of a human beta secretase molecule or molecular complex listed in Table 1.

7. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 5 wherein at least a portion of the points derived from the human beta secretase structure coordinates are derived from structure coordinates representing the locations of at least the backbone atoms of amino acids defining a human beta secretase binding pocket comprising the amino acids listed in Table 5.

8. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 7, wherein the binding pocket comprises the amino acids listed in Table 6.

9. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 7, wherein the binding pocket comprises the amino acids listed in Table 7.

10. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 5 displayed as a holographic image, a stereodiagram, a model or a computer-displayed image.

11. **(Withdrawn)** A scalable three-dimensional configuration of points, at least a portion of said points derived from structure coordinates of at least a portion of a human beta secretase molecular complex listed in Table 1 comprising at least one of a human beta secretase or beta secretase-like binding pocket.

12. **(Withdrawn)** A scalable three-dimensional configuration of points, at least a portion of the points derived from structure coordinates of at least a portion of a molecule or a molecular complex that is structurally homologous to a human beta secretase molecule or molecular

complex and comprises at least one of a human beta secretase or beta secretase-like binding pocket, wherein the human beta secretase molecule or molecular complex forms a crystal having the trigonal space group symmetry $P3_221$.

13. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 12 displayed as a holographic image, a stereodiagram, a model or a computer-displayed image

14. **(Withdrawn)** A machine-readable data storage medium comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of at least one glycosylated molecule or molecular complex selected from the group consisting of:

(i) a glycosylated molecule or molecular complex comprising at least a portion of a human beta secretase or beta secretase-like binding pocket comprising the amino acids listed in Table 5, the binding pocket defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 1;

(ii) a glycosylated molecule or molecular complex comprising at least a portion of a human beta secretase or beta secretase-like binding pocket comprising the amino acids listed in Table 6, the binding pocket defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 1; and

(iii) a glycosylated molecule or molecular complex that is structurally homologous to an human beta secretase molecule or molecular complex, wherein the human beta secretase molecule or molecular complex is represented by at least a portion of the structure coordinates listed in Table 1.

15. **(Withdrawn)** A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein said first set of data comprises a Fourier transform of at least a portion of the structural coordinates for human beta secretase listed in Table 1, wherein the human beta secretase molecule or molecular complex forms a crystal having unit cell dimensions $a=112.0 \pm 35 \text{ \AA}$, $b=112 \pm 35 \text{ \AA}$, $c=110 \pm 35 \text{ \AA}$, $\alpha=\beta=90^\circ$, $\gamma=120^\circ$; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex of unknown structure.

16. **(Withdrawn)** A method for obtaining structural information about a molecule or a molecular complex of unknown structure comprising:

crystallizing the molecule or molecular complex;

generating an x-ray diffraction pattern from the crystallized molecule or molecular complex; and

applying at least a portion of the structure coordinates for human beta secretase set forth in Table 1 to the x-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

17. **(Withdrawn)** A method for homology modeling an human beta secretase homolog comprising:

aligning the amino acid sequence of an human beta secretase homolog with an amino acid sequence of human beta secretase and incorporating the sequence of the human beta secretase homolog into a model of human beta secretase derived from human beta secretase structure coordinates set forth in Table 1 to yield a preliminary model of the human beta

secretase homolog, wherein the human beta secretase forms a crystal having unit cell dimensions $a=112.0 \pm 35 \text{ \AA}$, $b=112 \pm 35 \text{ \AA}$, $c=110 \pm 35 \text{ \AA}$, $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$;

subjecting the preliminary model to energy minimization to yield an energy minimized model; and

remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the human beta secretase homolog.

18. **(Withdrawn)** A computer-assisted method for identifying an inhibitor of human beta secretase activity comprising:

supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex that forms a crystal having the trigonal space group symmetry $P3_221$, the molecule or molecular complex comprising at least a portion of an human beta secretase or beta secretase-like binding pocket, the binding pocket comprising the amino acids listed in Table 5;

supplying the computer modeling application with a set of structure coordinates of a chemical entity; and

determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or molecular complex, wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of human beta secretase activity.

19. **(Withdrawn)** The method of claim 18 wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean square deviation of less than about 2.1 \AA from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 1.

20. **(Withdrawn)** The method of claim 18 wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean

square deviation of less than about 2.1 Å from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 3.

21. **(Withdrawn)** The method of claim 18 wherein determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or molecular complex comprises performing a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

22. **(Withdrawn)** The method of claim 18 further comprising screening a library of chemical entities.

23. **(Withdrawn)** A computer-assisted method for designing an inhibitor of human beta secretase activity comprising:

supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex that forms a crystal having unit cell dimensions $a=112.0 \pm 35$ Å, $b=112 \pm 35$ Å, $c=110 \pm 35$ Å, $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$, the molecule or molecular complex comprising at least a portion of a human beta secretase or beta secretase-like binding pocket, the binding pocket comprising the amino acids listed in Table 5;

supplying the computer modeling application with a set of structure coordinates for a chemical entity;

evaluating the potential binding interactions between the chemical entity and inhibitor binding pocket of the molecule or molecular complex;

structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and

determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or molecular complex, wherein binding to or interfering with the

molecule or molecular complex is indicative of potential inhibition of human beta secretase activity.

24. **(Withdrawn)** The method of claim 23 wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 1.

25. **(Withdrawn)** The method of claim 23 wherein determining whether the modified chemical entity is an inhibitor expected to bind to or interfere with the molecule or molecular complex comprises performing a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

26. **(Withdrawn)** The method of claim 23 wherein the set of structure coordinates for the chemical entity is obtained from a chemical fragment library

27. **(Withdrawn)** A computer-assisted method for designing an inhibitor of human beta secretase activity *de novo* comprising:

supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, the molecule or molecular complex comprising at least a portion of an human beta secretase or beta secretase-like binding pocket, wherein the inhibitor binding pocket comprises the amino acids listed in Table 5;

computationally building a chemical entity represented by set of structure coordinates; and

determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or molecular complex, wherein binding to or interfering with the molecule or

molecular complex is indicative of potential inhibition of human beta secretase activity.

28. **(Withdrawn)** The method of claim 27 wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 1.

29. **(Withdrawn)** The method of claim 27 wherein determining whether the chemical entity is an inhibitor expected to bind to or interfere with the molecule or molecular complex comprises performing a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex, followed by computationally analyzing the results of the fitting operation to quantify the association between the chemical entity and the binding pocket.

30. **(Withdrawn)** The method of any of claims 18, 23, or 27 further comprising supplying or synthesizing the potential inhibitor, then assaying the potential inhibitor to determine whether it inhibits human beta secretase activity.

31. **(Withdrawn)** A method for making an inhibitor of human beta secretase activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield an inhibitor of human beta secretase activity, the chemical entity having been identified during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a glycosylated molecule or molecular complex, the molecule or molecular complex comprising at least a portion of at least one of a human beta secretase or beta secretase-like binding pocket; supplying the computer modeling application with a set of structure coordinates of a chemical entity; and determining whether the chemical entity is expected to bind to or interfere with the molecule or molecular complex at a binding pocket,

wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of human beta secretase activity.

32. **(Withdrawn)** A method for making an inhibitor of human beta secretase activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield an inhibitor of human beta secretase activity, the chemical entity having been designed during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex that forms a crystal having unit cell dimensions $a=112.0 \pm 35 \text{ \AA}$, $b=112 \pm 35 \text{ \AA}$, $c=110 \pm 35 \text{ \AA}$, $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$, the molecule or molecular complex comprising at least a portion of at least one of a human beta secretase or beta secretase-like binding pocket; supplying the computer modeling application with a set of structure coordinates for a chemical entity; evaluating the potential binding interactions between the chemical entity and a binding pocket of the molecule or molecular complex; structurally modifying the chemical entity to yield a set of structure coordinates for a modified chemical entity; and determining whether the chemical entity is expected to bind to or interfere with the molecule or molecular complex at the binding pocket, wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of human beta secretase activity.

33. **(Withdrawn)** A method for making an inhibitor of human beta secretase activity, the method comprising chemically or enzymatically synthesizing a chemical entity to yield an inhibitor of human beta secretase activity, the chemical entity having been designed during a computer-assisted process comprising supplying a computer modeling application with a set of structure coordinates of a molecule or molecular complex, wherein the human beta secretase molecule or molecular complex forms a crystal having the trigonal space group symmetry $P3_221$ and the molecule or molecular complex comprises at least a portion of at least one of a human beta secretase or beta secretase-like binding pocket; computationally building a chemical entity

represented by set of structure coordinates; and determining whether the chemical entity is expected to bind to or interfere with the molecule or molecular complex at a binding pocket, wherein binding to or interfering with the molecule or molecular complex is indicative of potential inhibition of human beta secretase activity.

34. **(Withdrawn)** An inhibitor of human beta secretase activity identified, designed or made according to the method of any of the claims 18, 23, 27, 31, 32, or 33.

35. **(Withdrawn)** A composition comprising an inhibitor of human beta secretase activity identified or designed according to the method of any of the claims 18, 23, 27, 31, 32, or 33.

36. **(Withdrawn)** A pharmaceutical composition comprising an inhibitor of human beta secretase activity identified or designed according to the method of any of the 18, 23, 27, 31, 32, or 33 or a salt thereof, and pharmaceutically acceptable carrier.

37. **(Withdrawn)** A molecule or molecular complex that comprises at least a portion of a human beta secretase binding pocket, wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by the structure coordinates listed in Table 3.

38. **(Withdrawn)** The molecule or molecular complex of claim 37, wherein the binding pocket comprises the amino acids listed in Table 6.

39. **(Withdrawn)** The molecule or molecular complex of claim 37, wherein the binding pocket comprises the amino acids listed in Table 7.

40. **(Withdrawn)** A molecule or molecular complex that is structurally homologous to a human beta secretase molecule or molecular complex that forms a crystal having unit cell dimensions $a=112.0 \pm 35 \text{ \AA}$, $b=112 \pm 35 \text{ \AA}$, $c=110 \pm 35 \text{ \AA}$, $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$, wherein the human beta secretase molecule or molecular complex is represented by at least a portion of the structure coordinates listed in Table 3.
41. **(Withdrawn)** A scalable three-dimensional configuration of points, at least a portion of said points derived from structure coordinates of at least a portion of a human beta secretase molecule or molecular complex listed in Table 3 comprising at least one of a human beta secretase or beta secretase-like binding pocket, wherein the human beta secretase molecule or molecular complex forms a crystal having the trigonal space group symmetry $P3_221$.
42. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 41, wherein substantially all of said points are derived from structure coordinates of a human beta secretase molecule or molecular complex listed in Table 3.
43. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 41 wherein at least a portion of the points derived from the human beta secretase structure coordinates are derived from structure coordinates representing the locations of at least the backbone atoms of amino acids defining a human beta secretase binding pocket comprising the amino acids listed in Table 5.
44. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 43, wherein the binding pocket comprises the amino acids listed in Table 6.
45. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 43, wherein the binding pocket comprises the amino acids listed in Table 7.

46. **(Withdrawn)** The scalable three-dimensional configuration of points of claim 41 displayed as a holographic image, a stereodiagram, a model or a computer-displayed image.
47. **(Withdrawn)** A scalable three-dimensional configuration of points, at least a portion of said points derived from structure coordinates of at least a portion of a human beta secretase molecular complex listed in Table 3 comprising at least one of a human beta secretase or beta secretase-like binding pocket.
48. **(Withdrawn)** A machine-readable data storage medium comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of at least one molecule or molecular complex selected from the group consisting of:
- (i) a molecule or molecular complex comprising at least a portion of a human beta secretase or beta secretase-like binding pocket comprising the amino acids listed in Table 5, the binding pocket defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 3;
 - (ii) a molecule or molecular complex comprising at least a portion of a human beta secretase or beta secretase-like binding pocket comprising the amino acids listed in Table 6, the binding pocket defined by a set of points having a root mean square deviation of less than about 0.43 Å from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 3; and
 - (iii) a molecule or molecular complex that is structurally homologous to an human beta secretase molecule or molecular complex, wherein the human beta secretase molecule or molecular complex is represented by at least a portion of the structure coordinates listed in Table 3.

49. **(Withdrawn)** A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein said first set of data comprises a Fourier transform of at least a portion of the structural coordinates for human beta secretase listed in Table 3, wherein the human beta secretase molecule or molecular complex forms a crystal having unit cell dimensions $a=112.0 \pm 35 \text{ \AA}$, $b=112 \pm 35 \text{ \AA}$, $c=110 \pm 35 \text{ \AA}$, $\alpha=\beta=90^\circ$, $\gamma=120^\circ$; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex of unknown structure.

50. **(Withdrawn)** A method for obtaining structural information about a molecule or a molecular complex of unknown structure comprising:
crystallizing the molecule or molecular complex;
generating an x-ray diffraction pattern from the crystallized molecule or molecular complex; and
applying at least a portion of the structure coordinates for human beta secretase set forth in Table 3 to the x-ray diffraction pattern to generate a three-dimensional electron density map of at least a portion of the molecule or molecular complex whose structure is unknown.

51. **(Withdrawn)** A method for homology modeling an human beta secretase homolog comprising:
aligning the amino acid sequence of an human beta secretase homolog with an amino acid sequence of human beta secretase and incorporating the sequence of the human beta secretase homolog into a model of human beta secretase derived from human beta secretase structure coordinates set forth in Table 3 to yield a preliminary model of the human beta

secretase homolog, wherein the human beta secretase forms a crystal having unit cell dimensions $a=112.0 \pm 35 \text{ \AA}$, $b=112 \pm 35 \text{ \AA}$, $c=110 \pm 35 \text{ \AA}$, $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$;

subjecting the preliminary model to energy minimization to yield an energy minimized model; and

remodeling regions of the energy minimized model where stereochemistry restraints are violated to yield a final model of the human beta secretase homolog.

52. **(Withdrawn)** The method of claim 23 wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean square deviation of less than about 0.43 \AA from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 3.

53. **(Withdrawn)** The method of claim 27 wherein the binding pocket comprises the amino acids listed in Table 5, the binding pocket being defined by a set of points having a root mean square deviation of less than about 0.43 \AA from points representing the backbone atoms of said amino acids as represented by structure coordinates listed in Table 3.

54. **(Original)** A method for crystallizing a human beta secretase molecule or molecular complex comprising:
preparing purified human beta secretase in the presence of an inhibitor; and
crystallizing human beta secretase from a solution having a pH of about 3.5 to about 5.5.

55. **(Currently Amended)** The method of claim 59 ~~[[54]]~~ wherein the salt is selected from the group consisting of sodium chloride, ammonium sulfate, magnesium sulfate, lithium sulfate, and combinations thereof.

56. **(Original)** The method of claim 54 wherein the solution has a pH of about 4.0 to about 4.7.

57. **(Original)** The method of claim 54 wherein the solution comprises a buffer having a pK_a of about 3 to about 6.

58. **(Currently Amended)** The method of claim 66 ~~[[54]]~~ wherein the glycol is selected from the group consisting of PEG, PEG-MME, PEG-DME, polyoxyalkylenepolyamines, and combinations thereof.

59. **(Original)** The method of claim 54 wherein the solution further comprises a salt.

60. **(Original)** The method of claim 59 wherein the salt is present in a concentration of about 0.001 M to about 0.5 M.

61. **(Original)** The method of claim 54 wherein the solution includes up to about 40% by weight organic solvent.

62. **(Original)** The method of claim 61 wherein the organic solvent is DMSO.

63. **(Original)** The method of claim 54 wherein the solution further comprises up to about 40% by weight ethylene glycol or glycerol.

64. **(Original)** The method of claim 54 wherein the beta secretase is present at a concentration of about 1 mg/ml to about 80 mg/ml.

65. **(Original)** The method of claim 54 wherein the inhibitor is present at a concentration of about 0.1 to about 10 mM.

66. **(Original)** The method of claim 54 wherein the solution further comprises about 5% by weight to about 50% by weight of a glycol.

67. **(Original)** The method of claim 66 wherein the glycol is a monomeric or polymeric glycol.

68. **(Original)** The method of claim 54 wherein the human beta secretase is isolated from mammalian cells.

69. **(Original)** The method of claim 68 wherein the mammalian cells are CHO-K1 cells.

70. **(Original)** The method of claim 68 wherein the mammalian cells are HEK 293 cells.

71. **(Currently Amended)** The method of claim 54 wherein the human beta secretase is isolated from insect cells as part of a [[the]] Baculovirus expression system.

72. **(Original)** A crystal of beta secretase having the trigonal space group symmetry $P3_221$.

73. **(Original)** A crystal of beta secretase comprising a unit cell having dimensions of a, b, and c, wherein a is about 77 Å to about 147 Å, b is about 77 Å to about 147 Å, and c is about 77 Å to about 147 Å; and $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$.

74. **(Original)** A crystal of beta secretase having the trigonal space group symmetry $P3_221$ and comprising a unit cell having dimensions of a, b, and c, wherein a is about 77 Å to about 147

Å, b is about 77 Å to about 147 Å, and c is about 77 Å to about 147 Å; and $\alpha=\beta=90^\circ$, and $\gamma=120^\circ$.

75. **(Original)** The crystal of claim 74 having amino acid sequence SEQ ID NO:1.
76. **(Currently Amended)** The crystal of claim 74 ~~[[75]]~~ having amino acid sequence SEQ ID NO:1, with the proviso that at least one methionine is replaced with selenomethionine.
77. **(Withdrawn)** A method of producing human beta secretase, the method comprising expressing the human beta secretase in a mammalian cell line.
78. **(Withdrawn)** A method of producing human beta secretase, the method comprising expressing the human beta secretase in an insect cell line.